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Optical Coherence Tomography: Future Trends for Imaging in Glaucoma

Lindsey S. Folio, BS, Gadi Wollstein, MD, and Joel S. Schuman, MD

UPMC Eye Center, Eye & Ear Institute, Ophthalmology and Visual Science Research Center, Department of Ophthalmology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania (LSF, GW, JSS), and Department of Bioengineering, Swanson School of Engineering, University of Pittsburgh, Pittsburgh, Pennsylvania (LSF, JSS)

Abstract

Optical coherence tomography (OCT) captures a major role in clinical assessment in eye care. Innovative hardware and software improvements in the technology would further enhance its usefulness. In this review we present several promising initiatives currently in development or early phase of assessment that we expect to have a future impact on OCT.

Keywords

optical coherence tomography; OCT; image processing

Ophthalmic imaging technologies have greatly shaped the current clinical practice of eye care. The commercial technologies available today provide clinicians with high-resolution, real time images of the ocular structures involved in glaucoma and have the ability to quantify these structures. These capabilities are useful for identifying and monitoring diseases involving the retina^{1–11} and anterior segment.^{12–14}

The OCT technique was first published approximately 20 years ago¹⁵ and much improvement to the technology has since been made. OCT is a non-invasive imaging technique that utilizes low-coherence interferometry to create cross sectional images, using information from the echo time delay and reflected and backscattered light intensity. The most current iteration of OCT, spectral domain (SD)-OCT, has scanning speeds approximately 40–110 times faster than its predecessor,¹⁶ time domain (TD)-OCT, because it does not require the use of a moving mirror in the reference arm. SD-OCT transforms the signal into its frequency components, allowing all points of an axial scan (A-scan), sampling the tissue depth, to be collected simultaneously. Multiple A-scans are collected and segmentation algorithms are used to determine tissue layer boundaries and quantify retinal tissue thicknesses such as the retinal nerve fiber layer (RNFL). OCT has been shown to be reproducible in measuring retinal structures^{17–21} and has the ability to discriminate between healthy and glaucomatous eyes.^{22–24} Because of the advanced capabilities of OCT, it has become a primary imaging device in eye care allowing clinicians to monitor the progression of disease,^{25–27} visualize ocular structures in three dimensions (3D)^{28–30} and determine the effectiveness of clinical treatments.^{31, 32} Much of the current research in ophthalmic

Corresponding author: Gadi Wollstein, UPMC Eye Center, Department of Ophthalmology, University of Pittsburgh School of Medicine, 203 Lothrop Street, Eye and Ear Institute, Suite 834, Pittsburgh, PA 15213, wollsteing@upmc.edu.

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imaging focuses on improving SD-OCT, as well as developing multi-modal imaging systems that utilize other advanced optical techniques.

The focus of this paper is to discuss the projected developmental path of the OCT technology. The predicted impact this progress will have on imaging in the eye care clinic will also be discussed.

OCT IN GLAUCOMA: WHERE WE ARE

The first retinal OCT images were presented in 1991 and allowed visualization of the retinal layers and the optic nerve head (ONH).¹⁵ In 1995, the first OCT images of diseased retina were published, revealing an improved resolution of 10 μ m and showing the clinical utility of the device.^{5, 7} These studies revealed OCT's ability to quantify the retinal nerve fiber layer and showed non-invasive, non-contact visualization of macular pathologies such as epiretinal membranes, macular hole, and macular edema. In 2002, the first in-vivo SD-OCT images of the lens, iris, retina, and ONH were published.² Today, commercially available SD-OCT systems are capable of capturing images with scanning speeds of approximately 27,000 A-scans/second and axial resolutions of approximately 5–6 μ m, compared to TD-OCT systems with scanning speeds of approximately 400 A-scans/second and axial resolution of approximately 10 μ m. This improved performance allows SD-OCT to capture high-density images of the structures of the eye in 3D.

Both OCT technologies are available commercially and have shown the ability to reproducibly measure ocular tissue structures.^{17, 18, 21} In addition, measurements obtained with SD-OCT have been shown to offer improved reproducibility over TD-OCT measurements.³³ These devices employ normative databases that have the ability to highlight local defects,^{34, 35} and offer clinicians a more intuitive method to monitor disease status. TD and SD-OCT have also shown the ability to detect eyes defined as glaucomatous by visual fields.^{16, 22, 36–39} These imaging devices have shown the ability to detect glaucomatous progression in longitudinal studies.^{25–27, 40} In longitudinal assessment of glaucoma it is predicted that SD-OCT will offer more sensitivity and specificity for detecting change, compared to TD-OCT, because of the improved reproducibility and the ability to align scan location between visits. Further SD-OCT longitudinal studies need to be conducted before this can be confirmed.

PREDICTIONS FOR THE FUTURE

Imaging Methods

High-Speed—The eye presents as a near perfect environment to enable the use of OCT imaging. The pupil serves as a direct window to image structures of the retina and ONH, which are suitable for OCT because they are weakly scattering of light in the visible range. Even though the eye is very appropriate for the methodologies of OCT imaging, limitations continue to exist that may be overcome with improvements in image acquisition techniques. Currently, there has been an effort focused on increasing the scanning speed of OCT systems. Studies have shown OCT to be capable of achieving scanning speeds of up to 20.8 million A-scans/second.⁴¹ The benefits from increased scanning speeds are the reduction in eye movement associated with a shorter scanning time and the ability to employ signal averaging, where adjacent A-scans or B-scans are averaged. This has been shown to improve scan quality by reducing speckle noise⁴² and allow better visualization of retinal structure within OCT images.^{43, 44}

High-speed imaging also enables fine structures to be captured in high density, revealing important clinical information in micron scale. Studies have shown high-speed OCT systems

capable of presenting photoreceptor structures.^{45, 46} For visualization of the photoreceptors the use of high-speed OCT systems is required, otherwise small eye movements cause image distortion eliminating visualization of these microstructures. Faster scanning speeds would also allow the acquisition of 3D cubes of data that enable advanced processing. It allows novel scanning patterns, such as orthogonal scanning, to be performed, which have been shown to aid in reducing eye movement artifact through processing.⁴⁵ High speed imaging of the anterior chamber, cornea and lens, with a large imaging depth and high axial resolution, showed the ability to image mechanical processes in the anterior chamber, such as blinking and dilation.⁴⁷ This ability has potential for use in assessing the dynamics of the anterior segment.

Another form of Fourier domain OCT capable of scanning at high speed is swept source (SS) OCT.^{42, 48–50} SS-OCT also makes use of the Fourier transform to capture signals in the frequency domain; however, it employs a tunable laser and a single photodetector instead of a CCD camera. The utilization of a tunable laser allows the light to rapidly scan through the different appropriate frequencies in a broad spectrum, where the reflectance can then be assessed by a photodetector. The advantages of SS-OCT are that it does not result in signal drop-off with depth,¹⁶ and the imaging technique results in a high acquisition speed.⁵¹ Wide field imaging has been shown to be possible using an ultrahigh speed SS-OCT system. This method can capture images scanning a 12mm × 12mm area of retina at a sampling density of 1100 × 1100 A-scans.⁵¹ Wide field imaging offers the benefit of capturing both the ONH and macula regions in one image, which could potentially simplify and standardize ophthalmic examination protocols.

Longer Wavelengths—Currently, clinical OCT imaging of the retina mainly occurs at wavelengths in the 800–870nm range. In OCT imaging, to increase axial resolution the central wavelength can be decreased, the bandwidth can be increased, or a combination of the two can be performed. A low central wavelength light source provides a high axial resolution, however, it also leads to increased scattering of light, making deep penetration into the tissue difficult. An appropriate OCT light source must have a good balance between central wavelength and bandwidth to achieve the required axial resolution and scattering requirements. The current 800–870nm range is appropriate for achieving highly detailed images of the retina, however the melanin contained in the retinal pigment epithelial (RPE) is highly scattering and absorbing in this range,⁵² making it difficult to image structures below this tissue layer, such as the choroid and choriocapillaris. Additionally, due to the rapid signal drop off, the penetration of light into the optic nerve head is limited. Current research is focused on exploring OCT imaging at wavelengths of 1000 to 1100nm to achieve deeper imaging capabilities, and allow penetration below the RPE. Figure 1 shows an SD-OCT image using a 1030nm central wavelength light source, where C-mode segmentation highlights the lamina cribrosa pore structure. Long-wavelength imaging may also improve OCT signal quality in patients with media opacity.^{53, 54} High-speed retinal OCT in the 1000–1100nm wavelength range has been shown to allow imaging the layers of the choroid, useful in evaluation of glaucoma and age-related macular degeneration.⁵⁵ Moreover, the use of high-speed SS-OCT combined with a long wavelength light source has shown the ability to produce promising images of deep structures of the posterior segment, such as the lamina cribrosa and sclera.^{42, 49, 56}

Adaptive Optics—The transverse resolution of an OCT image is limited by the spot size of the beam of light, when focused on the retina. Optical aberrations, however, occur as light passes through the different media of the eye and limit the focusing power of the light. When OCT is combined with corrective optics techniques, such as adaptive optics, the spot size can be reduced, thus improving the transverse resolution of the imaging system. Adaptive optics (AO) imaging measures the monochromatic aberrations occurring in the eye

and corrects them using sensing of wavefronts and deformable mirrors. This technique has been shown to improve retinal imaging capabilities and can be combined with SD-OCT.^{57, 58} Here the combination of the high axial resolution of SD-OCT and enhanced transverse resolution of AO creates high-resolution images where visualization of retinal microvasculature and photoreceptors is possible.^{59–62} Limitations of AO include both its narrow depth of focus and small field of view, however the ability to align and stitch multiple AO frames together, creating a large mosaic retinal image has been shown.⁶³ Further studies are required on large cohorts to demonstrate the clinical impact of this combination imaging technique.

Image Analysis

Segmentation Algorithms—Current research in SD-OCT image analysis has focused on developing automatic segmentation algorithms to determine the thickness of individual layers of the retina including the retinal nerve fiber, retinal ganglion cell, plexiform, nuclear, and photoreceptor layers.⁶⁴ This microstructure can be visualized and quantified in SD-OCT images because of the superior axial resolution the device provides. With segmentation of the layers of the retina in SD-OCT scans, particularly in the macula region, improved glaucoma detection ability is realized. Additionally, when a 3D cube of data is captured and the retinal layers in each B-scan are segmented, a 2D thickness map can be created to represent each layer. This is accomplished by representing the thickness of the layer at a given point in the cube by a specific color on the thickness map.

In addition to using the segmentation methods to quantify retinal layers, a method called C-mode analysis can also be used to manually visualize the inner layers of an OCT cube scan.⁶⁵ This method of contour modeling provides the user with the ability to vary the thickness of the sampling plane as well as the contour the plane follows, as shown in Figure 1. It allows the image to be sectioned in a plane perpendicular to the scanning axis at any thickness to enable visualization of embedded structures. Figure 2 shows C-mode analysis of an eye with neuroretinal detachment, where the C-mode plane is shown at the RPE to highlight the damaged region. This method can also be useful in evaluating pathologies, such as macular edema and age-related macular degeneration that may result in failure if segmented with an automated algorithm. It has also been shown to provide better visualization of lamellar cribrosa pore structure when compared to optic disc photos,⁶⁶ which in the future may be relevant in the clinical evaluation of glaucoma. Because retinal diseases, such as macular edema and age-related macular degeneration, greatly disrupt the architecture of the retina, conventional OCT segmentation algorithms fail. Studies have shown the ability to employ automated algorithms to diagnose retinal pathologies based on 3D OCT data.^{67, 68}

Three-Dimensional Data—The high acquisition speed of SD-OCT allows 3D datasets to be collected and evaluated for clinical use. Here the volumetric structure of features such as the ONH and macula can be visualized and information obtained in the cube of data can be used in post-hoc analysis. Eye movement within 3D scans can cause inappropriate image interpretation and analysis. A reference image, such as the SLO image, can be used to correct for eye motion, by registering the OCT image to the SLO image.⁶⁹ An additional technique has been shown to correct for eye motion without the use of a reference image. This technique makes use of blood vessel location and aligns the A-scans and B-scans to remove eye movement by a particle filtering technique.⁷⁰ The ability to correct for eye movement in SD-OCT images would greatly improve the quality of the measurement analysis, especially for children and nystagmus patients, prone to movement during scanning. In addition, it can be expected to reduce the variability among consecutive scans thus improving the ability to detect progression.

The 3.4mm diameter circle continues to be used in glaucoma evaluation; however, with SD-OCT raster scans the circle can be placed in any location within the cube of data. Clinically, glaucoma progression detection with SD-OCT should not be limited to the 3.4mm circle, because local wedge defects could occur outside of this location, as shown in Figure 3. The entire cube of structural information should be utilized in the initial clinical evaluation and longitudinal follow-up. One technique to make use of the 3D data is to sum adjacent pixels into superpixels for comparison to normative superpixel data.⁷¹ These superpixel maps help highlight regions of decreased RNFL thickness, using the entire 3D cube of data, as shown in Figure 4. Further research is being performed to enhance the superpixel algorithms to maximize the sensitivity and specificity to detect glaucomatous damage and monitor change.

In addition to determining better use of 3D SD-OCT data there is a need for better 3D OCT viewing systems that offer cross-platform usability, so that OCT images from any commercially available device can be viewed on one monitor or hand-held device. There also is a need to allow clinicians to manipulate the 3D images to highlight a region of interest, instead of just being presented with a two-dimensional (2D) screen shot of a 3D image. The benefits offered through providing clinicians with the ability to virtually peel layers of the retina to highlight a certain pathology or disease cannot be quantified. An improved 3D viewing system would provide clinicians the ability to utilize the complete benefits of SD-OCT imaging in their clinical practice.

Retinal Blood Flow—Another method to use SD-OCT to evaluate aspects of ocular disease is to measure retinal blood flow. The ability to measure retinal blood flow in-vivo can provide insight on the pathogenesis of diseases, such as glaucoma and macular degeneration. Along with conventional structural scanning SD-OCT can acquire Doppler measurements from which flow velocities can be calculated and thus provide simultaneous structural and functional information. The light scattered from moving red blood cells creates a shift in the optical frequency of the light, which is related to the flow velocity. This provides a non-contact method to collect retinal flow information without the use of a contrast agent. Studies have shown SD-OCT's ability to monitor pulsatile blood flow in the retinal vessels.^{72, 73} A major limiting factor in this technique is the required measurement of the angle between the light source and the flow direction. Multiple studies have shown methods to overcome this barrier,^{74–76} however eye movement may limit the reliability of the measurements. Current studies are underway utilizing Doppler to assess blood flow involvement in diseases, such as glaucoma, branch retinal vein occlusion and diabetic retinopathies.^{77, 78} One study showed a trend in decreased blood flow velocity in eyes with retinal and optic nerve diseases when compared to normal eyes.⁷⁸ Further improvements in the SD-OCT methods employed to obtain blood flow measurements will be required before OCT parameters, such as blood flow velocity, can be used clinically.

OCT Imaging Applications

Animal Models—Utilizing OCT imaging in animal models is an application of the technology that continues to expand along with the imaging capabilities. Animal models have shown to be important in studying retinal diseases.^{79–83} Since OCT is non-invasive and allows tissue structure to be evaluated without histology, it makes longitudinal animal model evaluation possible and reduces the number of animals a study requires. Studies have shown OCTs ability to image rodent retina^{84, 85} and follow changes to mouse retinal thickness⁸⁶ and rat RNFL thickness⁸⁷ longitudinally in a glaucoma model. Studies have described the ability to automatically quantify the thickness of retinal tissue layers in rodents^{88, 89} and have evaluated the OCT en-face view of rats undergoing surgical elevation of intraocular pressure.⁹⁰ In larger animal models, SD-OCT imaging of macaque eyes has been used to delineate ocular structures,⁹¹ as well as evaluate changes to the deep structures of the ONH

longitudinally in an experimental glaucoma model.⁹² Further studies are required to truly realize the capabilities when combining animal models of disease with OCT imaging.

Surgical Guidance Systems—With the improved capabilities of SD-OCT also comes the ability to achieve high-resolution images of 3D structures in real-time. This ability has most recently been applied in developing OCT systems for use intraoperatively. Additionally, OCT units are now commercially available in handheld form enabling potential use during surgical ophthalmic manipulations. It has become standard practice for OCT images to be used in surgical planning for procedures such as those involving the anterior segment or macular holes, but now research is focused on developing OCT systems to use during surgical procedures. Improvement in the safety, ease and efficacy of the surgical treatment as well as receiving immediate feedback on ocular tissue manipulation is the main objective of this research.

The intraoperative use of OCT has been reported in various surgeries including corneal and retinal surgeries.^{93–98} In addition to using OCT clinically to evaluate ocular structures, studies have focused on improving the imaging techniques to better integrate OCT in the intraoperative environment. One group has shown the ability to present a virtual OCT image directly on the tissue of interest during surgery, removing the need for a separate OCT display.⁹⁹ Another group has developed a microscope mounted OCT technique, where the OCT and microscope share the same ocular path, making OCT visualization easier on the surgeon. They demonstrated vitreoretinal manipulations in a porcine eye and evaluated the interference of different surgical tools in the OCT image.¹⁰⁰ We expect to see rapid improvements in the techniques used to incorporate OCT visualization with ophthalmic surgery in the future.

CONCLUSIONS

Through this discussion we have explored the predicted future clinical use of OCT in eye care. There is still more work to be done to advance image acquisition techniques and improve the use of the OCT data in post processing, but it is currently underway. As these areas progress we expect to see the capabilities of OCT utilized to their full advantage in the clinic. Overall, we hope these advancements will improve the sensitivity and specificity of disease detection and progression monitoring, so that more timely and effective treatments can be implemented.

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Figure 1. SD-OCT image of optic nerve head in a healthy eye using a 1030nm central wavelength light source. (Right) B-scan showing segmentation plane. (Left) C-mode image highlighting the lamina pore structure.

Figure 2. Cirrus HD-OCT 200×200 macular cube scan showing the C-mode plane fit to the retinal pigment epithelial layer to highlight the region of neuroretinal detachment. A color version of this figure is available online at www.optvissci.com.

Figure 3. SD-OCT enface image (obtained from Cirrus HD-OCT 200×200 optic disc cube scan) showing 3.4mm diameter circle in purple and glaucomatous wedge defect in the inferotemporal region. The damage that is shown to be outside the normal range (red clusters) does not intersect the 3.4mm circle. A color version of this figure is available online at www.optvissci.com.

Figure 4.

Retinal nerve fiber layer (RNFL) thickness map of the peripapillary region, overlaid with superpixel analysis. (Left) Superpixel analysis of a healthy eye showing uniform clustering. (Right) Superpixel analysis of a glaucomatous eye showing smaller superpixels in areas of thin RNFL. A color version of this figure is available online at www.optvissci.com.